STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Randomized, Open Label Study to Evaluate the Efficacy and Safety of Tenofovir Alafenamide (TAF) versus Tenofovir Disoproxil Fumarate (TDF)–containing Regimens in Subjects with Chronic HBV Infection and Stage 2 or Greater Chronic Kidney Disease Who Have Received a Liver Transplant
Name of Test Drug:	Tenofovir Alafenamide (TAF)
Study Number:	GS-US-320-3912
Protocol Version (Date):	Amendment 2 (28 March 2017)
Analysis Type:	Week 24
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	19 March 2018
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase (SGPT)
Anti-HBe	antibody to HBeAg
Anti-HBs	antibody to HBsAg
AST	aspartate aminotransferase (SGOT)
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
bsAP	bone specific alkaline phosphatase
CDER	Center for Drug Evaluation and Research
CG	Cockcroft-Gault
CHB	chronic hepatitis B
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula for calculating glomerular filtration rate
C_{last}	last observed quantifiable concentration of the drug
CLCr	creatinine clearance
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau}, where "Dose" is the dose of the drug
C_{max}	maximum observed concentration of drug
CMH	Cochran-Mantel-Haenszel
CRF	case report form
C_{tau}	observed drug concentration at the end of the dosing interval
CTX	c-type collagen sequence
CV	coefficient of variation
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESDD	early study drug discontinuation
FAS	Full Analysis Set
FDA	Food and Drug Administration
$FEPO_4$	fractional excretion of filtered phosphate

FEUA	fractional excretion of uric acid
GFR	glomerular filtration rate
Gilead	Gilead Sciences, Inc.
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IVRS	interactive voice response system
IWRS	interactive web response system
LDL	low density lipoprotein
LLN	lower limit of the normal range
LLT	lower-level term
LOCF	last observation carried forward
M = E	Missing = Excluded
M = F	Missing = Failure
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
OC	osteocalcin
P1NP	procollagen type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic
pol/RT	polymerase/reverse transcriptase
PP	per protocol
PT	preferred term
Q	quartile
Q1	first quartile
Q3	third quartile
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class

$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate (Viread®)
TFLs	tables, figures, and listings
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve
TmP	tubular maximum reabsorption rate of phosphate
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the Week 24 Analysis for Study GS-US-320-3912. This SAP is based on the study protocol amendment 2 dated 28 March 2017 and the electronic case report form (eCRF). The SAP will be finalized before database finalization.

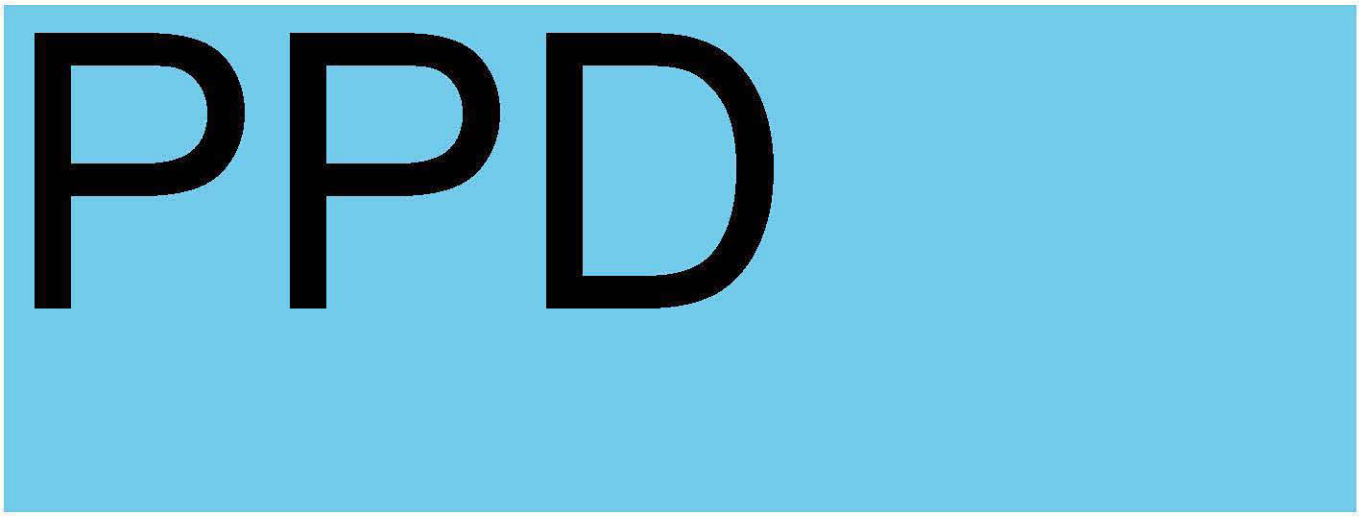
1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of TAF 25 mg once daily (QD) versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD-EPI}$ at Week 24
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 24

The secondary objectives of this study are as follows:

- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the percent change from baseline in hip and spine bone mineral density (BMD) at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in serum creatinine at Weeks 24 and 48
- To evaluate the safety of TAF 25 mg QD versus TDF-containing regimens as determined by the change from baseline in $eGFR_{CKD-EPI}$ at Week 48
- To evaluate the efficacy of TAF 25 mg QD versus TDF-containing regimens in maintaining viral suppression at Week 48



1.2. Study Design

This is a randomized, open-label, single center Phase 2 study to evaluate the safety and efficacy of TAF 25 mg QD versus TDF in adult chronic hepatitis B (CHB) infection subjects with Stage 2 or greater chronic kidney disease and have received a liver transplant.

Approximately 50 subjects will be randomized in a 1:1 ratio to either continue current treatment regimen with TDF alone or in combination with other approved antivirals or to receive TAF 25 mg per os (PO) daily. Approximately 40 of 50 subjects will be enrolled with $eGFR_{CKD\text{-}EPI}$ < 60 ml/min/1.73m^2. Randomization will be stratified by baseline renal function ($eGFR_{CKD\text{-}EPI}$ < 50 ml/min/1.73m^2 and ≥ 50 ml/min/1.73m^2)

- Treatment Arm A: approximately 25 subjects administered TAF 25 mg oral daily
- Treatment Arm B: approximately 25 subjects to continue administration of TDF alone or in combination with other approved antivirals as per local practice

The duration of the study treatment is 48 weeks with an initial screening period of 45 days. Subsequent to Screening, subjects will be randomized to receive TAF or TDF alone or in combination with approved antivirals per local practice.

PPD

If subjects choose PPD discontinue TAF prematurely, they will be followed for 24 weeks after the discontinuation of TAF (i.e., Treatment Free Follow-Up, TFFU) or until an alternative CHB treatment is started, whichever occurs first. In this SAP, the first 48 weeks of study treatment is referred to as randomized phase, PPD

The end of the study will be the last subjects' last observation or visit.

Laboratory analyses (serum chemistry, liver tests, hematology, plasma HBV DNA levels, pregnancy testing [for females of childbearing potential]), body weight, vital signs, adverse events (AEs), and concomitant medications will be performed at screening, baseline, week 4, 8, 12, 20, 24, every 12 weeks thereafter through Week 72, and every 24 weeks through PPD /ED visit.

HBV serology (qualitative HBsAg and HBeAg) will be performed at screening, baseline, Weeks 24, 48, PPD and ED. HBeAb and HBsAb testing will be performed as reflex testing as needed. Bone and renal biomarker testing will be performed at baseline and then at defined intervals throughout the study. Vitamin D assessments, FibroTest® and fasting metabolic assessments (fasting glucose and lipid panel) will be performed at baseline, Weeks 24, 48, PPD and PPD ED visit. Cr EDTA renal scan will be performed at baseline, Week 48 PPD visit.

Complete physical examinations will be performed at screening, baseline, and Weeks 12, 24, 48, PPD ED visit. Symptom directed physical examinations including body weight assessment will be conducted at all other visits. Dual energy x-ray absorptiometry (DXA) scans of the hip and spine should be performed during Screening and should be completed at least 14 days prior to the first dose of study drug, and will be conducted at Weeks 24, 48, PPD and the ED visit if not done within the last 24 weeks of this visit. Plasma, serum, and urine will be collected at baseline and at every visit thereafter for storage.

Follow-up assessments will occur every 4 weeks for 24 weeks and include the following: vital signs, hematology, serum chemistry, liver function tests, and plasma HBV DNA. PPD

1.3. Sample Size and Power

This is an exploratory study. No formal sample size calculation was performed.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee (DMC) Analysis

A data monitoring committee (DMC) will review the progress of the study and perform review of safety data once after 30 subjects have completed 12 weeks of treatment, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC may also provide recommendations as needed regarding study design. Subsequent meetings will be held on an ad hoc basis.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule. More details are documented in the independent DMC charter.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

2.2. Week 24 Analysis (Primary Analysis)

The Week 24 analysis will be conducted after the last subject completes the Week 24 visit or prematurely discontinues study drug.

2.3. Week 48 Analysis

The Week 48 analysis will be conducted after the last subject completes the Week 48 visit or prematurely discontinues study drug.

2.4. Final Analysis

The final statistical analysis for the study will be conducted after all subjects complete the study or prematurely discontinue study.

This statistical analysis plan (SAP) describes the analysis plan for the Week 24 analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the Randomized Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. Randomized Analysis Set

Randomized Analysis Set includes all subjects who were randomized in the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set (FAS)

The FAS will include all randomized subjects who have received at least 1 dose of study drug. Subjects will be analyzed according to the treatment to which they were randomized. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who have received at least 1 dose of study drug. Subjects will be analyzed according to the treatment they actually received during the randomized phase. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration. This is the primary analysis set for safety analyses.

3.1.4. Serologically Evaluable Full Analysis Set for HBsAg Loss/Seroconversion

The Serologically Evaluable Full Analysis Set for HBsAg loss/seroconversion will include all subjects who were randomized and had received at least 1 dose of study drug, and with HBsAg positive and HBsAb negative or missing at baseline. Subjects will be analyzed according to the treatment they were randomized to.

3.1.5. Serologically Evaluable Full Analysis Set for HBeAg Loss/Seroconversion

The Serologically Evaluable Full Analysis Set for HBeAg loss/seroconversion will include all subjects who were randomized and had received at least 1 dose of study drug, and with HBeAg positive and HBeAb negative or missing at baseline. Subjects will be analyzed according to the treatment they were randomized to.

3.1.6. DXA Analysis Set

3.1.6.1. Hip DXA Analysis Set

The Hip DXA Analysis Set will include all subjects who were randomized and had received at least 1 dose of study drug, and had nonmissing baseline hip BMD values. Subjects will be analyzed according to the treatment they actually received during the randomized phase.

3.1.6.2. Spine DXA Analysis Set

The Spine DXA Analysis Set will include all subjects who were randomized and had received at least 1 dose of study drug, and had nonmissing baseline spine BMD values. Subjects will be analyzed according to the treatment they actually received during the randomized phase.

3.1.7. Pharmacokinetic Analysis Set

The PK Analysis Set will include all randomized subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set for sparse PK analyses.

3.2. Subject Grouping

For efficacy analysis using FAS, subjects will be analyzed by randomized treatment. For safety analysis using the Safety Analysis Set, subjects will be analyzed by actual treatment received during the randomized phase.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- Screening renal function ($eGFR_{CKD-EPI}$ < 50 mL/ min/1.73m^2 and ≥ 50 mL/ min/1.73m^2)

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for efficacy and safety analysis.

3.5. Missing Data and Outliers

3.5.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for prior [disease-specific prior] and concomitant medications in Section 7.7.

3.5.2. Outliers

Outliers will be identified during data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analysis.

3.6. Data Handling Conventions and Transformations

Logarithm (base 10) will be used to transform HBV DNA data.

Natural logarithm transformation will be applied to PK concentrations and PK parameters such as C_{max}, C_{tau}, and AUC_{tau} for PK analysis.

PK concentration values below the limit of quantitation (BLQ) will be treated as 0 for the determination of summary and order statistics. Individual values that are BLQ will be presented as “BLQ” in the concentration data listing. For the presentation of summary and order statistics, if at least 1 subject has a concentration value BLQ for the time point, then the minimum value will be displayed as “BLQ”. If more than 50% of the subjects have a concentration data value BLQ for the time point, the minimum and median values will be displayed as “BLQ”. If all subjects have concentration data values BLQ for all the time points, all order statistics (minimum, first quartile [Q1], median, third quartile [Q3], and maximum) will be displayed as “BLQ”.

Data that are continuous in nature but are below the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows except for direct bilirubin, urine creatinine, and serum cystatin C:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (x is considered as the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively.

- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (x is considered as the limit of quantitation). Values with decimal points will follow the same logic as stated above.

- The limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "≤ x" or "≥ x" (x is considered as the limit of quantitation).

For direct bilirubin, a value of "< 0.1" is imputed as 0.09. For urine creatinine, a value of "< 1" is handled as a missing value in its summary and the calculation of related ratios. For serum cystatin C, a value of "< 0.10" is handled as a missing value in the calculation of estimated glomerular filtration rate (eGFR).

For HBV DNA, if the value in IU/mL (AMPLIPREP TAQM) is above the upper limit of quantification, the corresponding diluted value (AMPLIPREP TAQ), if available, will be used.

3.7. Analysis Visit Windows

3.7.1. Definition of Study Day

Study Day 1 is defined as the day when the first dose of study drug was taken, as recorded on the Study Drug Administration eCRF form.

Since the TDF group subjects are to continue administration of TDF alone or in combination with other approved antivirals as per local practice, for the TDF group the Study Day 1 is defined as: the first actual dose date on or after the latest lab or PK visit date with Baseline/Day 1 visit.

PPD

Study days are calculated relative to Study Day 1. For events that occurred on or after Study Day 1 date, study days are calculated as (visit date – Study Day 1 + 1). For events that occurred prior to Study Day 1, study days are calculated as (visit date – Study Day 1).

PPD

Follow-up days are for visits occurred during 24-week treatment-free follow-up period and calculated as (visit date – last dose date).

Last Dose Date of Randomized Drug is the latest non-missing end date of randomized drug, recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Discontinued" box checked for subjects who prematurely discontinued randomized drug or who completed randomized drug according to the Randomized Study Drug Completion eCRF. If the last dose date of randomized drug is missing (e.g., due to lost to follow up) for subjects who prematurely discontinued randomized drug, or for subjects who are still on randomized drug, the latest of non-missing randomized study drug start dates and end dates, the clinical visit dates and the laboratory visit dates excluding the dates of PPD 24-week treatment-free follow-up visits will be used to impute the last dose date of randomized drug.

For subjects who prematurely discontinued randomized study drug or who completed randomized study drug but did not enter optional treatment extension phase, the **Last Dose Date** is the same as Last Dose Date of Randomized Study Drug.

PPD

Last Study Date is the latest of non-missing study drug (randomized PPD phase) start dates and end dates, the clinic visit, the laboratory visit and DXA visit dates including the 24-week treatment-free follow-up visit date for subjects who prematurely discontinued study or who completed study according to Study Completion eCRF.

Baseline value for the randomized phase (except DXA BMD) is defined as the last non-missing value obtained on or prior to Study Day 1. For DXA BMD, the baseline value is defined as the last non-missing value on or prior to Study Day 14.

PPD

3.7.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The following windows (Table 3-1 to Table 3-5) apply to baseline and on-treatment assessments only. For summaries and analysis, assessments will first be categorized into baseline and on-treatment assessments occurring during the randomized PPD phase, before applying analysis windows.

For subjects who prematurely discontinued the randomized study drug PPD , laboratory assessments up to and including the last dose date of the randomized study drug + 3 days, and DXA assessments up to and including the last dose date of the randomized study drug + 14 days, will be considered as baseline or on-treatment during the randomized phase.

PPD

For subjects who have not discontinued the randomized study drug permanently, data collected up to database finalization date will be considered as baseline or on-treatment of the randomized phase.

PPD

For subjects who discontinue study drug early due to HBsAg loss with confirmed seroconversion, all efficacy data including data collected after the last dose date of the study drug will be reassigned analysis visits using the on-treatment assessment windows (Table 3-1, Table 3-2, and Table 3-4).

The analysis windows for HBV DNA, hematology, serum chemistry and liver function tests, eGFR (by CG and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]), renal biomarkers urine albumin to creatinine ratio (UACR), urine protein to creatinine ratio (UPCR), non-fasting glucose, weight, and vital sign assessments are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for HBV DNA, Hematology, Serum Chemistry and Liver Function Tests, eGFR (by CG and CKD-EPI), UACR, UPCR, Non-fasting Glucose, Weight, and Vital Sign Assessments

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	41
Week 8	56	42	69
Week 12	84	70	111
Week 20	140	112	153
Week 24	168	154	209
Week 36	252	210	293
Week 48	336	294	377

PPD

The analysis window for Fasting Glucose is in Table 3-2.

Table 3-2. Analysis Visit Windows for Fasting Glucose

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	55
Week 12	84	56	125
Week 24	168	126	251
Week 48	336	252	419

PPD

The analysis windows for BMD results from DXA, fasting and non-fasting lipid panel including direct low density lipoprotein (LDL), high density lipoprotein (HDL) and total cholesterol to HDL ratio, Fibrotest and HBV serology are presented in Table 3-3.

Table 3-3. Analysis Visit Windows for BMD Results from DXA, Fibrotest, Lipid Panel and HBV Serology

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1(14[a])
Week 24	168	2(15[a])	251
Week 48	336	252	503

PPD

a This applies to DXA only. Upper limit for baseline DXA BMD is Day 14 and lower limit for Week 24 DXA BMD is Day 15.

The analysis windows for Cr EDTA renal scan are presented in Table 3-4.

Table 3-4. Analysis Visit Windows for Cr EDTA Renal Scan

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1
Week 48	336	2	503

PPD

The analysis windows for renal biomarkers including urine retinol binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, and bone biomarkers including serum parathyroid hormone (PTH), C-type collagen sequence (CTX), procollagen type 1 N-terminal propeptide (P1NP), osteocalcin (OC), and bone specific alkaline phosphatase (bsAP) are presented in Table 3-5.

Table 3-5. Analysis Visit Windows for Renal and Bone Biomarkers

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	55
Week 12	84	56	125
Week 24	168	126	251
Week 48	336	252	419

PPD

Data collected after the last dose date will be considered as post-treatment visits. The analysis windows for post-treatment assessments are presented in Table 3-6.

Table 3-6. Analysis Visit Windows for Post Treatment Assessments

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Follow-Up Week 4	28	1	41
Follow-Up Week 8	56	42	69
Follow-Up Week 12	84	70	97
Follow-Up Week 16	112	98	125
Follow-Up Week 20	140	126	153
Follow-Up Week 24	168	154	181

3.7.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values are required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window. When a single value is needed, the following rule(s) will be used.

For baseline of the randomized phase, the last available record on or prior to the first dose of study drug will be selected. For DXA BMD, it is defined as the last value on or prior to Study Day 14. If there are multiple records with the same time or no time recorded on the same day for numeric observations, average will be computed for that day. If there are multiple records with the same time or no time recorded on the same day for categorical observations, the most conservative value will be taken, e.g., negative will be selected over positive for HBeAg and HBsAg, and positive will be selected over negative for HBeAb and HBsAb.

The following specified rules will be used for postbaseline visits:

- **ALT:** The largest value will be included in the analysis when 2 or more ALT values occur within the same visit window.
- **BMD:** The latest record in the window will be selected.
- **HBV DNA (IU/mL):** The record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected. If there is more than 1 record on the selected day, the geometric mean will be taken.
- **Serology:** For HBeAg, HBeAb, HBsAg, and HBsAb, the record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected. If there is more than 1 record on the selected day, the most conservative value will be taken, ie, positive will be selected over negative for HBeAg and HBsAg, and negative will be selected over positive for HBeAb and HBsAb.

For all other laboratory parameters:

- If multiple valid non-missing **numeric** observations exist in a window, then records will be chosen as follows:

  — The record closest to the nominal day for that visit will be selected. If there are 2 records equidistant from the nominal day, the latest will be selected. If there is more than 1 record on the selected day, the average will be taken.

- If multiple valid non-missing **categorical** observations (eg, safety ECG results) exist in a window, then records will be chosen as follows:

  — The most conservative value (eg, abnormal will be selected over normal for safety ECG) within the window will be selected. In the event that 2 values within a window are of equal abnormality, the value collected nearest to the nominal date will be used.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

The number and percentage of subjects enrolled in each randomization stratum will be summarized based on interactive voice response system/web response system (IXRS) data. If there are discrepancies between IXRS and screening laboratory data with regard to stratum assignment, a listing of the discrepancies will be provided.

The summary of subject disposition will be provided by treatment group and overall. This summary will include the number of subjects screened, screen failure subjects who were not randomized, subjects who met all eligibility criteria and were not randomized, subjects in the Randomized Analysis Set, subjects randomized but not treated, and subjects in the Safety Analysis Set.

In addition, the number and percentage of the subjects in the following categories will be summarized using the Safety Analysis Set:

Study Drug Completion

- Remaining on randomized study treatment
- Prematurely discontinued randomized study treatment (with summary of reasons for discontinuing treatment)
- Completed randomized study treatment
- PPD

Study Completion

- Entered 24-week treatment-free follow-up period
- Remaining on study
- Prematurely discontinued study (with summary of reasons for discontinuing study)
- Completed protocol-planned duration of the study

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to randomized study drug will be defined as (last dose date of randomized study drug – first dose date of randomized study drug + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to 1 decimal place, e.g., 4.5 weeks). If subjects are still on randomized study drug, the latest of randomized study drug start and end dates, and the clinic and laboratory visit dates (excluding the PPD treatment-free follow-up visit dates) will be used to impute the last dose date of randomized study drug for calculating the duration of randomized study drug exposure.

Duration of exposure to randomized study drug will be summarized using descriptive statistics (sample size, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, e.g., ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), etc.

Summaries will be provided by treatment group for subjects in the Safety Analysis Set.
No inferential statistics will be provided.

4.2.2. Adherence to Study Drug

Study drug regimen adherence will be computed based on tablet counts for the TAF group only. The numbers of tablets of study drug dispensed and returned are captured on study drug accountability forms.

Adherence (%) of study drug regimen will be calculated as follows:

$$\text{Adherence (\%)} = 100 \times \frac{\text{Number of tablets taken}}{\text{Number of tablets prescribed}}$$

$$= 100 \times \frac{\sum \text{No. of tablets taken at each dispensing period [1]}}{\sum \text{No. of tablets prescribed at each dispensing period [2]}}$$

[1] Number of tablets taken at a distinct dispensing period for a study drug is calculated as the minimum of (a) the daily number of tablets prescribed for the study drug multiplied by **the duration of treatment** at the dispensing period of the same dispensing date, and (b) the number of tablets taken for the study drug (number of tablets dispensed minus the number of tablets returned). Total number of tablets taken is determined by summing the number of tablets taken from all evaluable dispensing periods.

[2] Number of tablets prescribed at a distinct dispensing period for a study drug is calculated as the daily number of tablets prescribed for the study drug multiplied by **the duration of treatment** at the dispensing period of the same dispensing date. Total number of tablets prescribed is determined by summing the number of tablets prescribed from all evaluable dispensing periods.

The duration of treatment at a dispensing period for a study drug is calculated as the minimum of (a) the last returned date of the same dispensing period for the study drug, (b) date of premature discontinuation of the study drug, and (c) **next dispensing date** of the study drug, minus dispensing date of the study drug.

The next dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of tablets returned was missing (with "Yes" answered for "Was bottle returned?" question), it is assumed the number of tablets returned was 0. If the number of tablets dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown for the same dispensing date, then all records for the same dispensing date for that study drug will be excluded from both denominator and numerator calculation.

Adherence up to Week 24 visit will be calculated for each subject for the entire randomized dosing period up to the date of permanent discontinuation of the randomized study drug for subjects who prematurely discontinued randomized study drug or completed randomized study drug or using all data available for subjects remaining on randomized study drug.

The number and percentage of subjects who return at least 1 bottle and have calculable adherence during the study, descriptive statistics for adherence up to Week 24 visit for a study drug regimen (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of subjects belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided by treatment group for the Safety Analysis Set. No inferential statistics will be provided.

4.3. Protocol Deviations

A listing will be provided for subjects in the Randomized Analysis Set who violated at least 1 inclusion or exclusion criterion. The listing will include the unmet criteria. A listing of subjects who received the wrong study treatment will also be provided.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason will be summarized by treatment group for the Randomized Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic data (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of subjects for categorical data. Age is calculated as age in years at the first dose of study drug. The summaries of demographic data and baseline subject characteristics will be provided for the Safety Analysis Set.

5.2. Other Baseline Characteristics

- BMI categories (< 18.5 kg/m^2 [underweight], ≥ 18.5 - 25.0 kg/m^2 [normal], ≥ 25.0 - 30.0 kg/m^2 [overweight], and ≥ 30.0 kg/m^2 [obese])
- HBV DNA (IU/mL)
- ALT (U/L)
- ALT level based on central laboratory normal range (≤ ULN, > ULN - 5 × ULN, > 5 × ULN – 10 × ULN, > 10 ULN)
- ALT level based on American Association for the Study of Liver Diseases (AASLD) normal range with the ULN as 19 U/L for female and 30 U/L for male (≤ ULN, > ULN - 5 × ULN, > 5 × ULN - 10 × ULN, > 10 ULN)
- Estimated GFR by CG, CKD-EPI creatinine, and CKD-EPI Cystatin C methods
- HBeAg status (positive, negative)
- HBeAb status (positive, negative)
- Years positive for HBV
- Years of liver transplant
- Fibrotest score
- Fibrosis stage by fibrotest score (0 - 0.48, 0.49 - 0.74, 0.75 - 1)
- Proteinuria by urinalysis (dipstick) (Grade 0, Grade 1, Grade 2, Grade 3)
- Vitamin D

- Clinical BMD status (normal, osteopenia, osteoporosis)
- Hip fracture and major osteoporotic fracture probabilities estimated using FRAX® (see Section 7.3.4)

5.3. Medical History

A listing of medical history data will be provided for the Randomized Analysis Set.

6. EFFICACY ANALYSES

For Week 24 analyses, efficacy data will be summarized for the randomized phase (ie, up to Week 48), with the exception that summaries using M = F approach will be presented up to Week 24 only. All efficacy data up to the Week 24 data-cut including data collected during PPD treatment-free follow-up period will be listed.

6.1. Primary Efficacy Endpoints

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with HBV DNA < 20 IU/mL at Week 24.

6.1.2. Analysis of the Primary Efficacy Endpoint

The primary efficacy analysis will be conducted after the last randomized subject reaches Week 24 or discontinues study drug prematurely. An M = F approach will be employed. In this approach, all missing data will be treated as not achieving the primary endpoint (i.e., having HBV DNA ≥ 20 IU/mL).

6.1.3. Secondary Analysis for the Primary Efficacy Endpoint

Sensitivity analyses will be performed for the primary endpoint using Missing = Excluded (M = E) approach. In this approach, all missing data will be excluded in the computation (ie, missing data points will be excluded from both the numerator and denominator in proportion computation).

6.2. Other Efficacy Endpoints

6.2.1. Definition of Secondary and Other Efficacy Endpoints

The secondary efficacy endpoint is:

- The proportion of subjects with plasma HBV DNA < 20 IU/mL at Weeks 48

Other efficacy endpoints include:

- The proportion of subjects with normal ALT (by central laboratory and AASLD criteria) at Weeks 24 and 48
- The proportion of subjects with ALT normalization (by central laboratory and AASLD criteria) at Weeks 24 and 48
- The proportion of subjects with HBsAg loss at Weeks 24 and 48
- The proportion of subjects with HBeAg loss at Weeks 24 and 48

- The proportion of subjects with HBsAg seroconversion to anti-HBs at Weeks 24 and 48
- The proportion of subjects with HBeAg seroconversion to anti-HBe at Weeks 24 and 48
- The change from baseline in ALT at Weeks 24 and 48

The secondary endpoints at Weeks 48 will not be summarized using the primary analysis method (M=F) for the Week 24 analysis. Instead, they will be summarized at the next interim analyses at Weeks 48.

For the Week 24 analysis, the following definitions will be used:

- HBsAg loss is defined as HBsAg test result changes from HBsAg positive at baseline to HBsAg negative at a postbaseline visit with baseline HBsAb negative or missing
- HBeAg loss is defined as HBeAg test result changes from HBeAg positive at baseline to HBeAg negative at a postbaseline visit with baseline HBeAb negative or missing
- HBsAg seroconversion is defined as HBsAg loss and HBsAb test result changes from HBsAb negative or missing at baseline to HBsAb positive at a postbaseline visit
- HBeAg seroconversion is defined as HBeAg loss and HBeAb test result changes from HBeAb negative or missing at baseline to HBeAb positive at a postbaseline visit
- ALT normalization is defined as ALT > ULN (by central laboratory normal range or AASLD normal range) at baseline but within normal range at a postbaseline visit

Both baseline and postbaseline borderline serology results will be imputed using the following rules:

- HBsAg and HBeAg borderline will be considered as HBsAg positive and HBeAg positive
- HBsAb and HBeAb borderline will be considered as HBsAb negative and HBeAb negative

6.2.2. Analysis Methods for Secondary and Other Efficacy Endpoints

All the secondary and other efficacy endpoints involving proportions will be analyzed using the same statistical method (M = F) applied to the analysis of the primary efficacy endpoint. Sensitivity analyses will be performed using the M = E approach as well.

The change from baseline in ALT will be summarized by visit using observed data (ie, missing will be excluded).

In addition, the proportion of subjects with HBV DNA < 20 IU/mL and the proportion of subjects with normal ALT (by central laboratory and AASLD criteria, M = F) will be plotted with 95% CI over time for FAS. Median (Q1, Q3) and mean (95% CI) of change from baseline in ALT (U/L) will also be plotted over time using observed data for FAS.

6.3. Changes From Protocol-Specified Efficacy Analyses

Change from baseline in ALT was added in the SAP as other efficacy endpoints to fully explore the treatment effect of TAF versus TDF. Proportion of normal ALT and ALT normalization by visit evaluated using central laboratory and AASLD ULN, and proportion of subjects with HBsAg loss, HBeAg loss, HBsAg seroconversion and HBeAg seroconversion were also added.

All Randomized Analysis Set was not defined in the protocol but is added in the SAP.

7. SAFETY ANALYSES

For Week 24 analysis, safety data will be summarized for the randomized phase only (i.e., up to Week 48). All safety data up to the Week 24 data-cut including data collected during PPD 24-week treatment-free follow-up period will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

AEs are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life threatening) according to toxicity criteria specified in Appendix 5 of the clinical study protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of AEs to Study Drug

Related AEs are those for which the investigator answers "Yes" to the question "Related to Study Treatment?" in the eCRF. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purpose. Data listings will show relationship as missing.

7.1.4. Relationship of AEs to Study Procedure

AEs for which 'Yes' is marked for question 'Related to Study Procedures?' in the eCRF will be identified and included in AE listing.

7.1.5. Serious Adverse Events

Serious AEs are those identified as serious in the eCRF, where 'Yes' was marked for 'AE serious'. The clinical database will be reconciled with the serious AE database (from the Drug Safety and Public Health Department) before database finalization.

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs will be defined for the randomized phase and the extension phase separately.

Treatment-emergent AEs occurring during the randomized phase are defined as follows:

- Any AE with onset date on or after the randomized study drug start date and no later than the minimum of the randomized study drug stop date + 3 days PPD , for those who discontinued randomized study drug permanently, or
- Any AE with onset date on or after the randomized study drug start date for those who are still on the randomized study drug, or
- Any AE leading to randomized study drug discontinuation.

PPD

7.1.6.2. Incomplete Dates

If an AE onset date is incomplete or completely missing, the following rules will be used to define treatment-emergent AE:

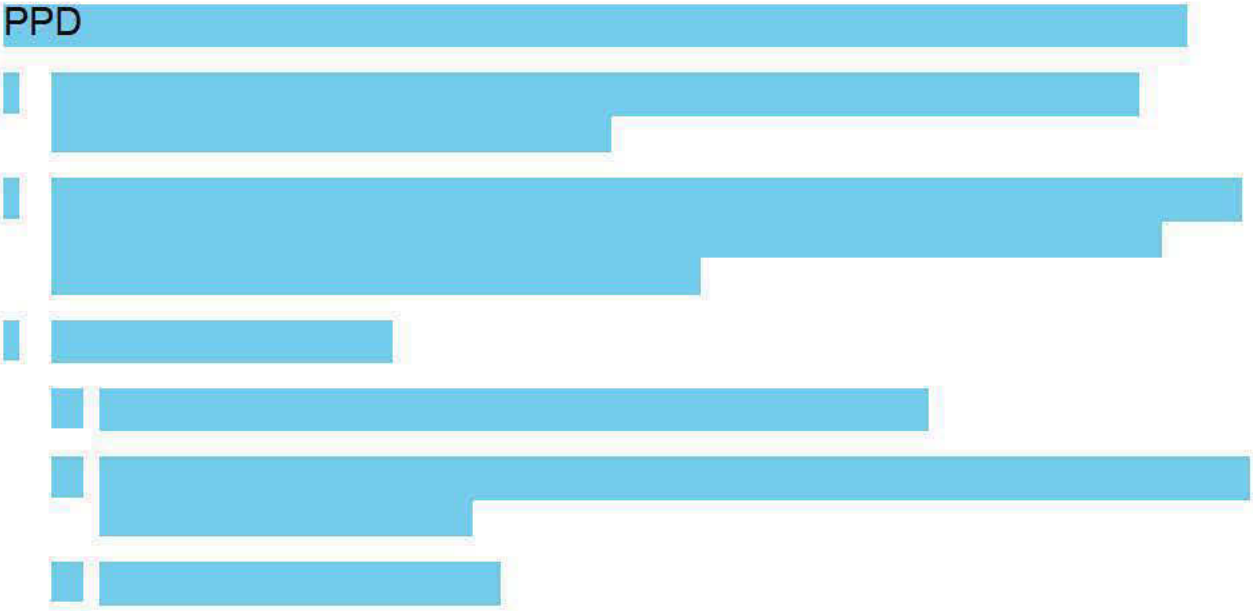
<u>Events with Missing Onset Day and/or Month</u>

The event is treatment-emergent during the randomized phase if the following criteria are met:

- The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of the randomized study drug, and
- For those who discontinued the randomized study drug permanently only: the month and year (or year) of onset date is the same as or before the month and year (or year) of the minimum of the randomized study drug stop date + 3 days PPD and

- AE End date is as follows:
  - The (complete) end date is on or after the first dose date of the randomized study drug, or
  - The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of randomized study drug, or
  - End date is completely missing

PPD

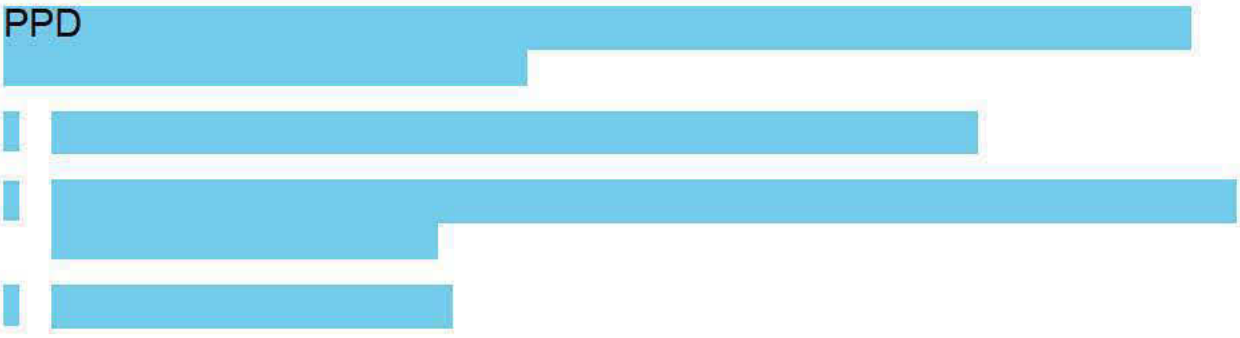


Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as treatment-emergent AE during the randomized phase if end date is as follows:

- The (complete) end date is on or after the first dose date of the randomized study drug, or
- The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of the randomized study drug, or
- End date is completely missing

PPD



7.1.7. Summaries of Adverse Events and Deaths

A brief summary of AEs (i.e., the number and percentage of subjects) will be presented by treatment group for the following: (1) any treatment-emergent AE, (2) any Grade 3 or 4 treatment-emergent AE, (3) any Grade 2, 3 or 4 treatment-emergent AE, (4) any treatment-emergent study drug-related AE, (5) any Grade 3 or 4 treatment-emergent study drug-related AE, (6) any Grade 2, 3 or 4 treatment-emergent study drug-related AE, (7) any treatment-emergent serious adverse event (SAE), (8) any treatment-emergent study drug-related SAE, (9) any treatment-emergent AE leading to premature study drug discontinuation, (10) any treatment-emergent AE leading to dose modification or study drug interruption, and (11) any death.

Treatment-emergent death during the randomized phase refers to death that occurs between the first dose date of the randomized study drug and the minimum of the last dose date of the randomized study drug + 3 days PPD , for those who discontinued randomized study drug permanently. PPD

Summaries (number and percentage of subjects) of AEs (by SOC, HLT [if specified below], and PT) will be provided by treatment group and overall using the Safety Analysis Set for the randomized phase as follows:

- All treatment-emergent AEs summarized by SOC, HLT, and PT
- Any Grade 3 or 4 treatment-emergent AEs
- Any Grade 2, 3, or 4 treatment-emergent AEs
- All treatment-emergent nonserious AEs occurring in at least 5% of subjects in any treatment group (this summary is generated per requirement for reporting in ClinicalTrials.gov)
- All treatment-emergent study drug-related AE summarized by SOC, HLT, and PT
- Any Grade 3 or 4 treatment-emergent study drug-related AEs
- Any Grade 2, 3, or 4 treatment-emergent study drug-related AEs
- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs leading to premature discontinuation from study drug
- All treatment-emergent AEs leading to dose modification or study drug interruption

Multiple events will be counted once only per subject in each summary. For data presentation, SOC (and HLT) will be ordered alphabetically, with PT sorted by decreasing total frequency. For summaries by severity grade, the most severe event will be selected.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All AEs
- Grade 3 and 4 AEs
- SAEs
- Study drug-related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug
- AEs leading to dose modification or study drug interruption

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the randomized phase based on Safety Analysis Set. Analysis will be based on values reported in conventional units. No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.2.1.1. Metabolic Assessments

Fasting lipid panel and fasting glucose measurements will not be summarized for the Week 24 analysis.

7.2.1.2. Calcium Correlated for Albumin

Calcium corrected for albumin will be calculated and summarized. The following formula will be used when both serum calcium and albumin results for a given blood draw are available and serum albumin value is < 4.0 g/dL.

Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 × (4.0 – albumin (g/dL)).

When albumin value is ≥ 4.0 g/dL, the actual calcium results will be used. Toxicity grading for calcium will be applied based on the corrected values.

7.2.2. Graded Laboratory Values

The criteria specified in the protocol will be used to grade laboratory results as Grade 0, Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life-threatening). Grade 0 includes all values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analysis for each direction (i.e., increased, decreased) will be presented separately.

For triglycerides, LDL, and total cholesterol, the protocol-specified toxicity grade scale is for fasting test values; non-fasting lipid results (or lipid results without known fasting status) will not be graded or summarized by toxicity grades.

If any laboratory toxicity grading scale overlaps with normal reference ranges (e.g., Grade 1 scale overlaps with normal reference ranges), laboratory values within normal range will not be graded except for lipid tests.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities occurring in the randomized phase are defined as values that increase by at least 1 toxicity grade from baseline at any postbaseline visit up to and including the minimum of the randomized study drug stop date + 3 days PPD , for those who discontinued randomized study drug prematurely, or values that increase by at least 1 toxicity grade from baseline at any postbaseline visit for those who are still on the randomized study drug. If the relevant baseline laboratory data are missing, any laboratory abnormality of at least Grade 1 will be considered treatment-emergent.

PPD

Fasting glucose and nonfasting glucose are graded based on different grading scales. Treatment-emergent laboratory abnormalities will be summarized for fasting glucose and nonfasting glucose separately.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities occurring in the randomized phase are defined as values that worsen by at least 3 grades from baseline at any postbaseline visit up to and including the minimum of the randomized study drug stop date + 3 days PPD for those who discontinued randomized study drug prematurely, or values that worsen by at least 3 grades from baseline at any postbaseline visit for those who are still on randomized study drug. If relevant baseline laboratory data are missing, any laboratory abnormalities of at least Grade 3 or 4 will be considered as treatment-emergent marked laboratory abnormalities.

PPD

7.2.2.3. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) of laboratory abnormalities will be provided by treatment group (subjects categorized according to most severe abnormality grade) for the randomized phase:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities
- Treatment-emergent marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with any non-missing postbaseline value in the given study period. A listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided.

7.2.3. ALT Elevation

An ALT elevation is defined as serum ALT > 2 × baseline value and > 10 × ULN, with or without associated symptoms. Confirmed ALT elevation (ALT flare) is defined as ALT elevations at 2 consecutive postbaseline visits. All treatment-emergent ALT elevations including confirmed ALT elevations will be summarized for the randomized phase. All treatment-emergent and nontreatment-emergent ALT elevations will be included in a listing.

If the first of two consecutive results is in the randomized phase and the second is out of the randomized phase (ie, in the PPD TFFU phase), then the result will be considered to be confirmed in the randomized phase (assuming both values meet the criterion). And if the criterion is met by the last value in the randomized phase and no assessments are available after due to the subject exiting the study or data not yet available, then the result will also be considered to be confirmed.

7.3. Bone Safety Analysis

7.3.1. Bone Mineral Density (BMD)

Percentage change from baseline in hip BMD and spine BMD will be summarized by treatment group and visit using descriptive statistics for subjects in the Hip and Spine DXA Analysis Sets, respectively.

Observed BMD values will be used for all the analyses described below.

For each subject and each visit, the clinical BMD status will be defined for hip and spine BMD based on the corrected t-score in Table 7-1.

Table 7-1. Normal, Osteopenia, and Osteoporosis as Defined by T-score

Clinical Status	BMD T-score
Normal	t-score $\geq$ -1.0
Osteopenia	-2.5 $\leq$ t-score < -1.0
Osteoporosis	t-score < -2.5

The number and percentage of subjects in each clinical BMD status (normal, osteopenia, and osteoporosis) will be summarized by visit and by baseline clinical status for both hip and spine.

The number and percentage of subjects in each category based on percentage change from baseline in hip BMD and spine BMD (> 7% decrease, > 5% to $\leq$ 7% decrease, > 3% to $\leq$ 5% decrease, > 1% to $\leq$ 3% decrease, > 0 to $\leq$ 1% decrease, 0 to $\leq$ 1% increase, > 1% to $\leq$ 3% increase, > 3% to $\leq$ 5% increase, > 5% to $\leq$ 7% increase, > 7% increase) will be summarized by treatment group and visit.

Median (Q1, Q3) and mean (95% CI) of percentage change from baseline in observed hip and spine BMD over time will be plotted by treatment group for the randomized phase. Listings of hip and spine DXA results will be provided.

7.3.2. Bone Biomarkers

Bone biomarkers include serum CTX, P1NP, PTH, OC, and bsAP.

Baseline, postbaseline, change from baseline, and percentage change from baseline in bone biomarkers will be summarized by treatment group and visit using descriptive statistics.

Median (Q1, Q3) percentage change from baseline in bone biomarkers over time will be plotted by treatment group. A listing of bone biomarker data will be provided.

7.3.3. Fracture Events

The PTs for fracture events were defined based on both Standardized MedDRA Query (SMQ) of Osteoporosis/Osteopenia and HLGT of Fractures from MedDRA 20.0 (see Appendix 1). Treatment-emergent fracture events will be summarized based on the identified PTs from SMQ alone and both SMQ and HLGT combined. The number and percentage of subjects who experienced fracture events will be summarized by treatment group for the randomized phase. A data listing of fracture events will be provided.

7.3.4. Assessment of Fracture Probability

Fracture probabilities will be assessed using FRAX®, a computer based algorithm developed by the World Health Organization (WHO; http://www.shef.ac.uk/FRAX).

The FRAX algorithm is based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck. The algorithm provides both the 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip, or shoulder fracture).

The FRAX model is constructed from real data in population-based cohorts around the world that have a limited age range. For an age below 40 or above 90 years, the tool will calculate the probability of fracture at the age of 40 or 90 years, respectively. Due to the age limitation, 2 sets of analyses of fracture probabilities will be performed.

In the first set of analysis, summaries of baseline and change from baseline in the 10-year probabilities of hip fracture, as well as major osteoporotic fracture will be presented by treatment group and visit for subjects aged between 40 and 90 years for the randomized phase.

In the second set of analysis, the above-specified analysis will be performed to include all subjects, where subjects with an age below 40 or above 90 years will be treated as having an age of 40 or 90 years, respectively, in computing their fracture probabilities.

Data listings of fracture risk assessment questionnaire and FRAX fracture probabilities will be provided.

7.3.5. Bone Events

The PTs for bone events were defined by selecting relevant bone PTs based on MedDRA 20.1 (see Appendix 2). The number and percentage of subjects who experienced treatment-emergent bone events will be summarized by treatment group for the randomized phase. A data listing of bone events will be provided.

7.4. Renal Safety Analysis

7.4.1. Confirmed Renal Abnormalities

Confirmed renal abnormalities are defined as follows:

- Confirmed increase from baseline in creatinine of at least 0.5 mg/dL or
- Baseline $eGFR_{CKD\text{-}EPI} \geq 50$ mL/min/1.73 m^2 and confirmed postbaseline $eGFR_{CKD\text{-}EPI} < 50$ mL/min/1.73 m^2 or
- Confirmed phosphorous < 2 mg/dL

Treatment-emergent confirmed renal abnormalities will be summarized for randomized phase. All confirmed renal abnormalities including those occurred during PPD 24-week treatment-free follow-up period will be listed.

7.4.2. Serum Creatinine

The baseline and change from baseline in serum creatinine at Week 24 will be summarized using descriptive statistics. Change from baseline in observed serum creatinine by visit will be analyzed similarly.

Median (Q1, Q3) and mean (95% CI) of change from baseline in observed serum creatinine over time will be plotted by treatment group.

7.4.3. Estimated Glomerular Filtration Rate

The following formulae will be used to calculate eGFR:

- CG:

  $eGFR_{CG}$ (mL/min) = [(140 – age (yrs)) × weight (kg) × (0.85 if female)] / (SCr (mg/dL) × 72),

  where weight is actual total body mass in kilograms, and SCr is serum creatinine.

- CKD-EPI Creatinine Based:

  $eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 m^2) = 141 × min(SCr/κ,1)$^{\alpha}$ × max(SCr/κ,1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if black),

  where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1 {Levey 2009}.

- CKD-EPI Cystatin C based:

  $eGFR_{CKD\text{-}EPI,\ cysC}$ (mL/min/1.73 m^2) = 133 × min(SCys/0.8, 1)$^{-0.499}$ × max(SCys/0.8, 1)$^{-1.328}$ × 0.996^{age} [× 0.932 if female],

  where SCys is serum cystatin C.

Change from baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ at each postbaseline visit will also be provided during the randomized phase.

The number and proportion of subjects with decrease from baseline of ≥ 25% and ≥ 50% in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ will be summarized by treatment groups for the randomized phase.

The baseline and postbaseline $eGFR_{CKD\text{-}EPI,\ cysC}$ with percentage change from baseline will be listed.

Median (Q1, Q3) change from baseline in $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$ over time will be plotted for the randomized phase.

7.4.4. Treatment-emergent Proteinuria (Dipstick)

Treatment-emergent proteinuria by urinalysis (dipstick) will be summarized by treatment group for the randomized phase. A listing of subjects with treatment-emergent proteinuria will be provided.

7.4.5. Urine RBP to Creatinine Ratio and Beta 2 Microglobulin to Creatinine Ratio

Baseline, postbaseline, change from baseline and percentage change from baseline in urine RBP to creatinine ratio and beta-2-microglobulin to creatinine ratio will be summarized by treatment group and visit using descriptive statistics. Median (Q1, Q3) percentage change from baseline over time will be plotted by treatment group for the randomized phase.

7.4.6. Proteinuria by Quantitative Assessment

Baseline, postbaseline, changes from baseline, and percentage change from baseline in UPCR and UACR will be summarized by treatment group and visit using descriptive statistics, for the randomized phase.

The number and proportion of subjects with UPCR ≤ 200 mg/g versus > 200 mg/g will be summarized by baseline category for each postbaseline visit during the randomized phase {KDIGO Guideline Development Staff 2013}.

The number and proportion of subjects with UACR < 30 mg/g versus ≥ 30 mg/g will be summarized by baseline category for each postbaseline visit during the randomized phase {KDIGO Guideline Development Staff 2013}.

Median (Q1, Q3) percentage change from baseline over time will be plotted by treatment group for the randomized phase.

7.4.7. Other Renal Biomarkers

Other renal biomarkers include TmP/GFR, $FEPO_4$, and FEUA.

TmP/GFR based on serum creatinine {Barth 2000} will be calculated as follows:

$$TmP/GFR = TRP \times SPO_4 \quad if\ TRP \le 0.86$$
$$TmP/GFR = 0.3 \times TRP / \left[1 - (0.8 \times TRP)\right] \times SPO_4 \quad if\ TRP > 0.86$$

where TRP (tubular reabsoprtion of phosphate) is calculated by:

$$TRP = 1 - \frac{UPO_4}{SPO_4} \times \frac{SCr}{UCr}$$

where SCr is serum creatinine concentration (mg/dL), UPO_4 is urine phosphate concentration (mg/dL), SPO_4 is serum phosphate concentration, and UCr is urine creatinine concentration (mg/dL).

Urine $FEPO_4$ will be calculated as follows:

$$FEPO_4\ (\%) = (SCr \times UPO_4) / (SPO_4 \times UCr) \times 100\ (\%)$$

Urine FEUA will be calculated as follows:

$$FEUA\ (\%) = (SCr \times UUa) / (SUa \times UCr) \times 100\ (\%)$$

where UUa and SUa are urine and serum uric acid (mg/dL), respectively.

The baseline, postbaseline, and change from baseline in TmP/GFR, $FEPO_4$, and FEUA will be summarized by treatment group and visit using descriptive statistics during the randomized phase.

In addition, the baseline, postbaseline, and change from baseline of corrected surface area value from EDTA renal scan will be summarized by treatment group and visit using descriptive statistics during the randomized phase.

7.5. Body Weight

Body weight at each visit and change from baseline in body weight will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group for each postbaseline analysis window. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.6. Prior Hepatitis B Medications

Prior HBV medications will be summarized by treatment group. No inferential statistics will be computed. A listing of prior HBV medications will also be provided.

7.7. Concomitant Medications

Concomitant medications (ie, medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary.

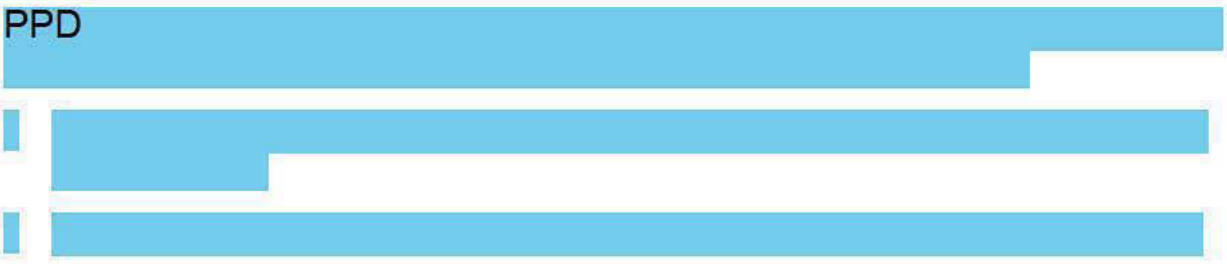
For the Week 24 analysis, summaries of concomitant medications using the number and percentage of subjects for each treatment group will be provided for the randomized phase based on the Safety Analysis Set and by WHO generic name. Subject will be counted only once for each generic name. The summary will be ordered by overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

If the start or stop date of concomitant medications is incomplete, the month and year (or year alone if month is not recorded) of start or stop date will be used to determine if the medications are concomitant as follows.

The medication is concomitant for the randomized phase if the month and year of start or stop (or year of the start or stop) of the medication do not meet any of following criteria:

- The month and year of start of the medication is after the date of the last dose of randomized study drug
- The month and year of stop of the medication is before the date of the first dose of randomized study drug

PPD



If the start and stop date of the medications are not missing, and the start date is not after the last dose date of the randomized study drug and the stop date is not before the first dose date of the randomized study drug, or the medications are marked as ongoing and start date is on or before the last dose date of the randomized study drug, the medications are considered concomitant during the randomized phase.

PPD

No inferential statistics will be provided. Subjects with any concomitant medication use will also be listed.

7.8. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy during the study.

7.9. Changes From Protocol-Specified Safety Analyses

Treatment-emergent AE and lab abnormality in randomized phase was defined as any AE or lab abnormality that begins on or after the first dose date of study drug up to the last dose date in the protocol, and is updated in this SAP. Treatment-emergent AE occurring in the randomized phase is defined as any AE with onset date on or after the first dose date of the randomized study and no later than the minimum of the randomized study drug stop date + 3 days PPD , if applicable for the randomized phase. Treatment-emergent laboratory abnormalities occurring in the randomized phase are defined as values that increase by at least 1 toxicity grade from baseline at any postbaseline visit up to and including the minimum of the randomized study drug stop date + 3 days PPD for the randomized phase. This change was made as labs performed 1-2 days after study drug stopped were being excluded causing the measurement for the timepoint to be missed, even though protocol specified visit windows allowed for labs to be performed in a short period after the study drug was stopped.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

A single PK blood sample will be collected at any time during each On-Treatment Visit for all subjects up to week 48 to measure TAF and TFV concentrations

PPD

8.2. Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times (elapsed time) before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Post dose samples that are BLQ will be imputed at one-half of the lower limit of quantitation (LLOQ). The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

PK parameters that may be estimated in this substudy are listed and defined in Table 8-1.

Table 8-1. PK Parameters

Parameter	Description
AUC_{last}	The area under the concentration versus time curve from time 0 to the last quantifiable concentration
AUC_{tau}	The area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
C_{tau}	observed drug concentration at the end of the dosing interval
CL/F	apparent oral clearance after administration of the drug: at steady state: CL/F = Dose/$AUC_{tau,}$ where "Dose" is the dose of the drug
$T_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_z/F	apparent volume of distribution of the drug
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve

8.3. Statistical Analysis Methods

Individual subject plasma concentration data and individual subject PK parameter will be listed and summarized using descriptive statistics. The descriptive statistics (sample size, mean, SD, coefficient of variation [% CV], minimum, median, maximum, Q1, Q3, geometric mean, and its 95% CI, will be presented for plasma concentration data and individual PK parameters.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as zero at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

For some PK parameter data (ie, C_{max}, C_{tau}, C_{last}, AUC_{tau} and AUC_{last}), the geometric mean, its 95% CI, and the mean and SD of the natural-log transformed values will be presented in addition to the summaries mentioned above.

The following TFLs will be provided for analytes for intensive PK analysis at the Week 4 or Week 8 visits (summarization is for PK Substudy Analysis Set):

- Table with individual subject concentration data and summary statistics at each time point for each analyte
- Table with individual subject PK parameters and summary statistics for each analyte (for PK Substudy Analysis Sets only)

- Mean (SD) concentration vs time figures – linear and semi-log plots for TAF and TFV (for PK Substudy Analysis Sets only)

- Median (Q1, Q3) concentration vs time figures – linear and semi-log plots for TAF and TFV (for PK Substudy Analysis Sets only)

The following TFLs will be provided for analytes for sparse PK from Week 4 through Week 24 visits (summarization is for PK Analysis Set):

- Table with individual subject concentration data and summary statistics at each visit for each analyte.

- Mean (SD) concentration vs visit figures – linear and semi-log plots for TAF and TFV (for PK Analysis Sets only).

The following listings will be provided for general PK analysis from Week 4 through Week 48 for the randomized analysis set:

- Listing of PK sampling details

- Listing of study drug administration record for PK dosing

The listings of PK sample details and study drug administration record for the intensive PK substudy and single PK samples will be combined for presentation.

9. REFERENCES

Barth JH, Jones RG, Payne RB. Calculation of renal tubular reabsorption of phosphate: the algorithm performs better than the nomogram. Ann Clin Biochem 2000;37 (Pt 1):79-81.

KDIGO Guideline Development Staff. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney international. Supplement 2013;3 (1):v-150.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150 (9):604-12.

10. SOFTWARE

SAS® (SAS Institute Inc., Version 9.4, Cary, NC) is to be used for all programming of tables, listings, and figures.

Phoenix WinNonlin® (Pharsight Corporation Version 7.0, Mountain View, CA) is to be used for all PK analyses.

FRAX® (WHO Collaborating Center for Metabolic Bone Disease, University of Sheffield, UK) is to be used for the 10-year probabilities of hip fracture or a major osteoporotic fracture.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Fracture Events

The selected PTs of fracture events from SMQ of Osteoporosis/Osteopenia and HLGT of Fractures are listed as follows:

	Selected Preferred Terms	Selection Type
1	Acetabulum fracture	cSMQ+cHLGT
2	Ankle fracture	cHLGT
3	Atypical femur fracture	cSMQ+cHLGT
4	Atypical fracture	cHLGT
5	Avulsion fracture	cHLGT
6	Bone fissure	cHLGT
7	Bone fragmentation	cHLGT
8	Cervical vertebral fracture	cSMQ+cHLGT
9	Chance fracture	cHLGT
10	Clavicle fracture	cHLGT
11	Closed fracture manipulation	cSMQ
12	Comminuted fracture	cHLGT
13	Complicated fracture	cHLGT
14	Compression fracture	cHLGT
15	Craniofacial fracture	cHLGT
16	Epiphyseal fracture	cHLGT
17	External fixation of fracture	cSMQ
18	Facial bones fracture	cHLGT
19	Femoral neck fracture	cSMQ+cHLGT
20	Femur fracture	cSMQ+cHLGT
21	Fibula fracture	cHLGT
22	Flail chest	cHLGT
23	Foot fracture	cHLGT
24	Forearm fracture	cSMQ+cHLGT
25	Fracture	cSMQ+cHLGT
26	Fracture displacement	cHLGT
27	Fracture of clavicle due to birth trauma	cHLGT
28	Fracture treatment	cSMQ
29	Fractured coccyx	cHLGT
30	Fractured ischium	cSMQ+cHLGT
31	Fractured sacrum	cSMQ+cHLGT
32	Fractured skull depressed	cHLGT
33	Greenstick fracture	cHLGT
34	Hand fracture	cHLGT
35	Hip fracture	cSMQ+cHLGT
36	Humerus fracture	cHLGT
37	Ilium fracture	cSMQ+cHLGT
38	Impacted fracture	cHLGT

	Selected Preferred Terms	Selection Type
39	Internal fixation of fracture	cSMQ
40	Jaw fracture	cHLGT
41	Limb fracture	cHLGT
42	Lisfranc fracture	cHLGT
43	Lower limb fracture	cHLGT
44	Lumbar vertebral fracture	cSMQ+cHLGT
45	Multiple fractures	cSMQ+cHLGT
46	Open fracture	cHLGT
47	Open reduction of fracture	cSMQ
48	Open reduction of spinal fracture	cSMQ
49	Osteochondral fracture	cHLGT
50	Osteoporotic fracture	cSMQ+cHLGT
51	Patella fracture	cHLGT
52	Pathological fracture	cSMQ+cHLGT
53	Pelvic fracture	cSMQ+cHLGT
54	Periprosthetic fracture	cHLGT
55	Pubis fracture	cSMQ+cHLGT
56	Radius fracture	cSMQ+cHLGT
57	Rib fracture	cSMQ+cHLGT
58	Sacroiliac fracture	cSMQ+cHLGT
59	Scapula fracture	cHLGT
60	Scapulothoracic dissociation	cHLGT
61	Skull fracture	cHLGT
62	Skull fractured base	cHLGT
63	Spinal compression fracture	cSMQ+cHLGT
64	Spinal fracture	cSMQ+cHLGT
65	Sternal fracture	cHLGT
66	Stress fracture	cHLGT
67	Tartrate-resistant acid phosphatase decreased	cSMQ
68	Thoracic vertebral fracture	cSMQ+cHLGT
69	Tibia fracture	cHLGT
70	Torus fracture	cHLGT
71	Traumatic fracture	cHLGT
72	Ulna fracture	cHLGT
73	Upper limb fracture	cHLGT
74	Vertebroplasty	cSMQ
75	Wrist fracture	cSMQ+cHLGT
76	Vertebral body replacement	cSMQ

Appendix 2. Bone Events

The selected PTs of bone events based on MedDRA 20.1 are listed as follows:

	Selected Preferred Terms
1	Subchondral insufficiency fracture
2	Metaphyseal corner fracture
3	Fracture infection
4	Acetabulum fracture
5	Ankle fracture
6	Atypical femur fracture
7	Atypical fracture
8	Avulsion fracture
9	Bone fissure
10	Bone fragmentation
11	Cervical vertebral fracture
12	Chance fracture
13	Clavicle fracture
14	Comminuted fracture
15	Complicated fracture
16	Compression fracture
17	Costal cartilage fracture
18	Craniofacial fracture
19	Epiphyseal fracture
20	Facial bones fracture
21	Femoral neck fracture
22	Femur fracture
23	Fibula fracture
24	Flail chest
25	Foot fracture
26	Forearm fracture
27	Fracture
28	Fracture blisters
29	Fracture delayed union
30	Fracture displacement

	Selected Preferred Terms
31	Fracture malunion
32	Fracture nonunion
33	Fracture of clavicle due to birth trauma
34	Fractured coccyx
35	Fractured ischium
36	Fractured sacrum
37	Fractured skull depressed
38	Greenstick fracture
39	Hand fracture
40	Hip fracture
41	Humerus fracture
42	Ilium fracture
43	Impacted fracture
44	Jaw fracture
45	Limb fracture
46	Lisfranc fracture
47	Lower limb fracture
48	Lumbar vertebral fracture
49	Multiple fractures
50	Open fracture
51	Osteochondral fracture
52	Osteoporotic fracture
53	Patella fracture
54	Pathological fracture
55	Pelvic fracture
56	Periprosthetic fracture
57	Pseudarthrosis
58	Pubis fracture
59	Radius fracture
60	Rib fracture
61	Sacroiliac fracture
62	Scapula fracture
63	Scapulothoracic dissociation

	Selected Preferred Terms
64	Skull fracture
65	Skull fractured base
66	Spinal compression fracture
67	Spinal fracture
68	Spinal fusion fracture
69	Sternal fracture
70	Stress fracture
71	Thoracic vertebral fracture
72	Tibia fracture
73	Torus fracture
74	Traumatic fracture
75	Ulna fracture
76	Upper limb fracture
77	Wrist fracture
78	Bone formation test
79	Bone formation test abnormal
80	Bone metabolism biochemical marker increased
81	Bone resorption test
82	Bone resorption test abnormal
83	C-telopeptide
84	C-telopeptide increased
85	Deoxypyridinoline urine
86	Deoxypyridinoline urine increased
87	N-telopeptide
88	N-telopeptide urine
89	N-telopeptide urine abnormal
90	N-telopeptide urine decreased
91	N-telopeptide urine increased
92	N-telopeptide urine normal
93	Osteocalcin
94	Osteocalcin decreased
95	Osteocalcin increased
96	Osteoprotegerin

	Selected Preferred Terms
97	Osteoprotegerin decreased
98	Osteoprotegerin increased
99	Osteoprotegerin ligand
100	Osteoprotegerin ligand decreased
101	Pyridinoline urine
102	Pyridinoline urine decreased
103	Pyridinoline urine increased
104	Tartrate-resistant acid phosphatase
105	Tartrate-resistant acid phosphatase decreased
106	Alveolar osteitis
107	Aneurysmal bone cyst
108	Bone callus excessive
109	Bone contusion
110	Bone cyst
111	Bone development abnormal
112	Bone disorder
113	Bone erosion
114	Bone fistula
115	Bone formation decreased
116	Bone formation increased
117	Bone hyperpigmentation
118	Bone infarction
119	Bone lesion
120	Bone loss
121	Callus formation delayed
122	Cemento osseous dysplasia
123	Cystic angiomatosis
124	Dental alveolar anomaly
125	Dental cyst
126	Enostosis
127	Erdheim-Chester disease
128	Exostosis
129	Exostosis of external ear canal

	Selected Preferred Terms
130	Exostosis of jaw
131	Exposed bone in jaw
132	Extraskeletal ossification
133	Hyperphosphatasaemia
134	Hypertrophic osteoarthropathy
135	Inadequate osteointegration
136	Jaw cyst
137	Jaw disorder
138	Jaw fistula
139	Medial tibial stress syndrome
140	Melorheostosis
141	Osteitis
142	Osteitis condensans
143	Osteitis deformans
144	Osteonecrosis
145	Osteonecrosis of external auditory canal
146	Osteonecrosis of jaw
147	Osteoradionecrosis
148	Osteorrhagia
149	Osteosclerosis
150	Osteosis
151	Periosteal haematoma
152	Periostitis
153	Periostitis hypertrophic
154	Periostosis
155	Periprosthetic osteolysis
156	Post transplant distal limb syndrome
157	Post-traumatic osteoporosis
158	Primary sequestrum
159	Radiation osteitis
160	Secondary sequestrum
161	Skeletal injury
162	Spinal column injury

	Selected Preferred Terms
163	Spinal disorder
164	Sternal injury
165	Tertiary sequestrum
166	Vertebral column mass
167	Vertebral lesion
168	Vertebral wedging
169	Bone atrophy
170	Itai-itai disease
171	Bone decalcification
172	Bone metabolism disorder
173	Brown tumour
174	Chronic kidney disease-mineral and bone disorder
175	Craniotabes
176	Gorham's disease
177	Hereditary hypophosphataemic rickets
178	High turnover osteopathy
179	Hungry bone syndrome
180	Hypochondroplasia
181	Hypophosphataemic rickets
182	Low turnover osteopathy
183	Oncogenic osteomalacia
184	Osteolysis
185	Osteomalacia
186	Osteopenia
187	Osteoporosis
188	Osteoporosis circumscripta cranii
189	Osteoporosis postmenopausal
190	Osteoporotic fracture
191	Rachitic rosary
192	Resorption bone decreased
193	Resorption bone increased
194	Rickets
195	Senile osteoporosis

	Selected Preferred Terms
196	Spinal compression fracture
197	Bone marrow oedema
198	Bone marrow oedema syndrome
199	Bone pain
200	Bone swelling
201	Coccydynia
202	Eagle's syndrome
203	Metatarsalgia
204	Os trigonum syndrome
205	Pain in jaw
206	Pubic pain
207	Spinal pain
208	Astragalectomy
209	Bone cyst excision
210	Bone debridement
211	Bone electrostimulation therapy
212	Bone graft
213	Bone graft removal
214	Bone lesion excision
215	Bone operation
216	Bone prosthesis insertion
217	Bone trimming
218	Cementoplasty
219	Epiphyseal surgery
220	Epiphysiodesis
221	Orthopaedic procedure
222	Ostectomy
223	Osteomyelitis drainage
224	Osteopathic treatment
225	Osteosynthesis
226	Osteotomy
227	Removal of epiphyseal fixation
228	Removal of internal fixation

	Selected Preferred Terms
229	Sequestrectomy
230	Calcification metastatic
231	Parathyroid hyperplasia
232	Gastric mucosal calcinosis
233	Calciphylaxis
234	Calcium deficiency
235	Calcium intoxication
236	Calcium metabolism disorder
237	Chondrocalcinosis pyrophosphate
238	Chvostek's sign
239	Dent's disease
240	Familial hypocalciuric hypercalcaemia
241	Hypercalcaemia
242	Hypercalcaemia of malignancy
243	Hypercalcaemic nephropathy
244	Hypercalcitoninaemia
245	Hypercalciuria
246	Hypocalcaemia
247	Hypocalcaemic seizure
248	Hypocalciuria
249	Hypoparathyroidism
250	Hypoparathyroidism secondary
251	Latent tetany
252	Neonatal hypocalcaemia
253	Periarthritis calcarea
254	Primary familial brain calcification
255	Primary hypoparathyroidism
256	Pseudohypercalcaemia
257	Pseudohypoparathyroidism
258	Tetany
259	Tooth demineralisation
260	Trousseau's sign
261	Williams syndrome

	Selected Preferred Terms
262	Congenital syphilitic osteochondritis
263	Epiphyseal disorder
264	Epiphyseal injury
265	Epiphyses delayed fusion
266	Epiphyses premature fusion
267	Epiphysiolysis
268	Epiphysitis
269	Closed fracture manipulation
270	External fixation of fracture
271	Fracture debridement
272	Fracture reduction
273	Fracture treatment
274	Fractured maxilla elevation
275	Fractured zygomatic arch elevation
276	Internal fixation of fracture
277	Intramedullary rod insertion
278	Open reduction of fracture
279	Skeletal traction
280	Surgical fixation of rib fracture
281	Ankle fracture
282	Atypical femur fracture
283	Clavicle fracture
284	Epiphyseal fracture
285	Femoral neck fracture
286	Femur fracture
287	Fibula fracture
288	Foot fracture
289	Forearm fracture
290	Fracture of clavicle due to birth trauma
291	Greenstick fracture
292	Hand fracture
293	Hip fracture
294	Humerus fracture

	Selected Preferred Terms
295	Limb fracture
296	Lisfranc fracture
297	Lower limb fracture
298	Osteochondral fracture
299	Patella fracture
300	Radial head dislocation
301	Radius fracture
302	Scapula fracture
303	Scapulothoracic dissociation
304	Tibia fracture
305	Torus fracture
306	Ulna fracture
307	Upper limb fracture
308	Wrist fracture
309	Amputation
310	Arm amputation
311	Calcanectomy
312	Finger amputation
313	Finger repair operation
314	Foot amputation
315	Foot operation
316	Gluteoplasty
317	Hand amputation
318	Hand repair operation
319	Hip disarticulation
320	Interscapulothoracic amputation
321	Leg amputation
322	Limb amputation
323	Limb immobilisation
324	Limb operation
325	Limb reattachment surgery
326	Limb reconstructive surgery
327	Metacarpal excision

	Selected Preferred Terms
328	Metatarsal excision
329	Microsurgery to hand
330	Rotationplasty
331	Talipes correction
332	Toe amputation
333	Toe operation
334	Trapeziectomy
335	Alveolar bone resorption
336	Itai-itai disease
337	Bone atrophy
338	Bone decalcification
339	Bone metabolism disorder
340	Brown tumour
341	Chronic kidney disease-mineral and bone disorder
342	Dwarfism
343	High turnover osteopathy
344	Hungry bone syndrome
345	Low turnover osteopathy
346	Oncogenic osteomalacia
347	Osteodystrophy
348	Osteolysis
349	Osteomalacia
350	Osteopenia
351	Osteoporosis
352	Osteoporosis circumscripta cranii
353	Osteoporosis postmenopausal
354	Renal rickets
355	Resorption bone decreased
356	Resorption bone increased
357	Rickets
358	Senile osteoporosis
359	Aspiration bursa
360	Aspiration bursa abnormal

	Selected Preferred Terms
361	Aspiration bursa normal
362	Aspiration joint
363	Aspiration joint abnormal
364	Aspiration joint normal
365	Biopsy abdominal wall
366	Biopsy abdominal wall abnormal
367	Biopsy abdominal wall normal
368	Biopsy bone
369	Biopsy bone abnormal
370	Biopsy bone normal
371	Biopsy cartilage
372	Biopsy cartilage abnormal
373	Biopsy cartilage normal
374	Biopsy chest wall
375	Biopsy chest wall abnormal
376	Biopsy chest wall normal
377	Biopsy ligament
378	Biopsy ligament abnormal
379	Biopsy ligament normal
380	Biopsy muscle
381	Biopsy muscle abnormal
382	Biopsy muscle normal
383	Biopsy soft tissue
384	Biopsy tendon
385	Biopsy tendon abnormal
386	Biopsy tendon normal
387	Intervertebral disc biopsy
388	Synovial biopsy
389	Synovial biopsy abnormal
390	Synovial fluid cell count
391	Synovial fluid crystal
392	Synovial fluid crystal present
393	Synovial fluid red blood cells

	Selected Preferred Terms
394	Synovial fluid red blood cells positive
395	Synovial fluid white blood cells
396	Synovial fluid white blood cells positive
397	Arthrogram
398	Arthrogram abnormal
399	Arthrogram normal
400	Arthroscopy
401	Arthroscopy abnormal
402	Arthroscopy normal
403	Bone densitometry
404	Bone density abnormal
405	Bone density decreased
406	Bone density increased
407	Bone scan
408	Bone scan abnormal
409	Bone scan normal
410	Discogram
411	Discogram abnormal
412	Discogram normal
413	Face and mouth X-ray
414	Face and mouth X-ray abnormal
415	Face and mouth X-ray normal
416	Orthoroentgenogram
417	Skeletal survey
418	Skeletal survey abnormal
419	Skeletal survey normal
420	Skull X-ray
421	Skull X-ray abnormal
422	Skull X-ray normal
423	Spinal X-ray
424	Spinal X-ray abnormal
425	Spinal X-ray normal
426	Ultrasound joint

	Selected Preferred Terms
427	X-ray limb
428	X-ray limb abnormal
429	X-ray limb normal
430	X-ray of pelvis and hip
431	X-ray of pelvis and hip abnormal
432	X-ray of pelvis and hip normal
433	Acetabulum fracture
434	Fractured ischium
435	Ilium fracture
436	Pelvic fracture
437	Pubis fracture
438	Sacroiliac fracture
439	Acute phosphate nephropathy
440	Hyperphosphataemia
441	Hyperphosphaturia
442	Hypophosphataemia
443	Phosphorus metabolism disorder
444	Pseudohyperphosphataemia
445	Renal rickets
446	Craniofacial fracture
447	Facial bones fracture
448	Fractured skull depressed
449	Jaw fracture
450	Skull fracture
451	Skull fractured base
452	Cervical vertebral fracture
453	Chance fracture
454	Dislocation of vertebra
455	Fractured coccyx
456	Fractured sacrum
457	Intervertebral disc injury
458	Lumbar vertebral fracture
459	Spinal compression fracture

	Selected Preferred Terms
460	Spinal fracture
461	Spinal fusion fracture
462	Thoracic vertebral fracture
463	Atypical femur fracture
464	X-ray dental abnormal
465	Carpal collapse
466	Osteonecrosis
467	Osteonecrosis of external auditory canal
468	Osteonecrosis of jaw
469	Osteoradionecrosis
470	Abscess jaw
471	Abscess oral
472	Alveolar osteitis
473	Arthrodesis
474	Biopsy bone abnormal
475	Bone abscess
476	Bone debridement
477	Bone graft
478	Bone infarction
479	Bone loss
480	Bone pain
481	Bone scan abnormal
482	Candida osteomyelitis
483	Chronic recurrent multifocal osteomyelitis
484	Dental necrosis
485	Exposed bone in jaw
486	Face and mouth X-ray abnormal
487	Groin pain
488	Hip arthroplasty
489	Hip surgery
490	Jaw fistula
491	Jaw lesion excision
492	Jaw operation

	Selected Preferred Terms
493	Joint arthroplasty
494	Joint prosthesis user
495	Joint resurfacing surgery
496	Maxillofacial operation
497	Oral surgery
498	Oroantral fistula
499	Osteitis
500	Osteoarthropathy
501	Osteomyelitis
502	Osteomyelitis acute
503	Osteomyelitis bacterial
504	Osteomyelitis blastomyces
505	Osteomyelitis chronic
506	Osteomyelitis drainage
507	Osteomyelitis fungal
508	Osteomyelitis salmonella
509	Osteomyelitis viral
510	Osteotomy
511	Pain in jaw
512	Periodontal destruction
513	Primary sequestrum
514	Resorption bone increased
515	Secondary sequestrum
516	Sequestrectomy
517	Staphylococcal osteomyelitis
518	Subperiosteal abscess
519	Tertiary sequestrum
520	Tooth abscess
521	Tooth infection
522	X-ray limb abnormal
523	X-ray of pelvis and hip abnormal
524	Bone density decreased
525	Serum procollagen type I N-terminal propeptide decreased

	Selected Preferred Terms
526	Subchondral insufficiency fracture
527	Bone formation decreased
528	Bone loss
529	Bone marrow oedema syndrome
530	Osteopenia
531	Osteoporosis
532	Osteoporosis postmenopausal
533	Osteoporotic fracture
534	Resorption bone increased
535	Senile osteoporosis
536	Acetabulum fracture
537	Atypical femur fracture
538	Body height abnormal
539	Body height below normal
540	Body height decreased
541	Bone density abnormal
542	Bone formation test abnormal
543	Bone metabolism biochemical marker increased
544	Bone metabolism disorder
545	Bone resorption test abnormal
546	Cervical vertebral fracture
547	Closed fracture manipulation
548	C-telopeptide increased
549	Deoxypyridinoline urine increased
550	External fixation of fracture
551	Femoral neck fracture
552	Femur fracture
553	Forearm fracture
554	Fracture
555	Fracture treatment
556	Fractured ischium
557	Fractured sacrum
558	Hip arthroplasty

	Selected Preferred Terms
559	Hip fracture
560	Hip surgery
561	Ilium fracture
562	Internal fixation of fracture
563	Kyphoscoliosis
564	Kyphosis
565	Lumbar vertebral fracture
566	Multiple fractures
567	N-telopeptide urine increased
568	Open reduction of fracture
569	Open reduction of spinal fracture
570	Osteocalcin increased
571	Osteoporosis prophylaxis
572	Pathological fracture
573	Pelvic fracture
574	Post-traumatic osteoporosis
575	Pubis fracture
576	Pyridinoline urine increased
577	Radius fracture
578	Rib fracture
579	Sacroiliac fracture
580	Spinal compression fracture
581	Spinal deformity
582	Spinal fracture
583	Tartrate-resistant acid phosphatase decreased
584	Thoracic vertebral fracture
585	Vertebral body replacement
586	Vertebroplasty
587	Wrist fracture
588	Wrist surgery
589	Ankle arthroplasty
590	Ankle operation
591	Arthrectomy

	Selected Preferred Terms
592	Arthrolysis
593	Arthroscopic surgery
594	Arthrotomy
595	Baker's cyst excision
596	Bone groove deepening
597	Bunion operation
598	Capsulorrhaphy
599	Delayed spinal fusion
600	Elbow operation
601	Epiphyseal injury
602	Flail chest
603	Incomplete spinal fusion
604	Knee arthroplasty
605	Knee operation
606	Ligament operation
607	Maxillonasal dysplasia
608	Meniscus operation
609	Meniscus removal
610	Patella replacement
611	Patellectomy
612	Radiolucency around implant
613	Radiotherapy to joint
614	Removal of foreign body from joint
615	Rheumatoid nodule removal
616	Rotator cuff repair
617	Shoulder arthroplasty
618	Shoulder operation
619	Synovectomy
620	Synoviorthesis
621	Temporomandibular joint surgery
622	Tophus removal operation